



Using the Patient Concerns Inventory in the identification of fatigue following treatment for head and neck cancer

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International Journal of Oral & Maxillofacial Surgery

Using the PCI in the identification of fatigue following treatment for head and neck cancer

--Manuscript Draft--

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Abstract:	<p>Fatigue has a profound impact on health-related quality of life (HRQOL) and the aim of this study is to describe the clinical characteristics and HRQOL for head and neck cancer patients who raise the issue of fatigue on the Patient Concerns Inventory (PCI), at their review consultation. Eight consultants were randomised to use the PCI as part of a cluster-controlled trial. Patients also completed the UW-QoLv4 (University of Washington Quality of Life), EQ-5D-5L (EuroQol Group) and Distress Thermometer. There were 140 patients who attended clinics at a median (IQR) of 108 (70-165) days after the end of treatment. The PCI item 'fatigue' was the 6th most commonly selected, by 29% (40). Those with advanced tumours were more likely (36% 30/83 Vs 18% 10/56, $p=0.02$) to have selected the item, as were those treated with radiotherapy +/- chemotherapy (39% 34/87 Vs 11% 6/53, $p<0.001$). The PCI fatigue group reported significantly worse overall QOL, social-emotional and physical function composite scores, distress thermometer, and EQ-5D. PCI-fatigue was common in those with sleeping, nausea, mood, depression, mobility, breathing and energy level concerns. In conclusion, given the problems associated with fatigue, it is appropriate to screen and seek interventions that might help patient address this.</p>

International Journal of Oral & Maxillofacial Surgery

30th August 2020

Editor-in-Chief

Professor Nabil Samman

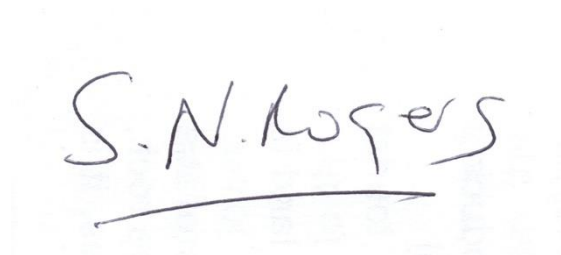
Dear Nabil,

Please find a paper entitled '**Using the PCI in the identification of fatigue following treatment for head and neck cancer**'.

The matter of fatigue following head and neck cancer is a very important issue and the trial as given us the opportunity to raise the issue.

Thank you so much for your consideration.

Yours sincerely

A handwritten signature in dark ink, reading 'S. N. Rogers', with a horizontal line drawn underneath it.

Simon N Rogers

On behalf of the other co-authors:

Dr Cherith J Semple Institute of Nursing and Health Research, Ulster University.

Professor Gerald M Humphris School of Medicine, St Andrews University.

Mr Derek Lowe Medical Statistician, Director, Astraglobe Ltd.

Professor Anastasios Kanatas, Leeds Teaching Hospitals and St James Institute of Oncology.

Journal: INTERNATIONAL JOURNAL OF
ORAL & MAXILLOFACIAL SURGERY

Title of Paper:

Using the PCI in the identification of fatigue
following treatment for head and neck cancer

Declarations

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned to you. If you have nothing to declare in any of these categories then this should be stated.

Please state any conflict of interests. A conflict of interest exists when an author or the author's institution has financial or personal relationships with other people or organisations that inappropriately influence (bias) his or her actions. Financial relationships are easily identifiable, but conflicts can also occur because of personal relationships, academic competition, or intellectual passion. A conflict can be actual or potential, and full disclosure to The Editor is the safest course.

Competing Interests

None

Please state any sources of funding for your research

This trial is funded by the RfPB on behalf of the NIHR (**PB-PG-0215-36047**).

DOES YOUR STUDY INVOLVE HUMAN OR ANIMALSUBJECTS? Please cross out whichever is not applicable

YES

If your study involves human or animal subjects or records of human patients you MUST have obtained ethical approval. Ethics approval or exemption are required for retrospective studies on patients' records

Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number. A COPY OF THE ETHICAL APPROVAL OR EXEMPTION LETTER MUST BE UPLOADED WITH YOUR SUBMISSION

The PCI trial has ethical approval from North West - Liverpool Central Research Ethics Committee REC reference: IRAS 16/NW/0465, Project ID: 189554. It also has approval from the Health Research Authority (HRA). The Research and Development Department at Aintree University Hospital NHS Trust (AUH) is coordinating the trial and AUH is the sponsor for the trial.

Patient Consent – please state whether written patient consent has been obtained. Please note that patient consent is always required to publish clinical photographs. If patient consent was not required, please state this. The Journal may request a copy of this consent prior to acceptance

Consent was given by patients as part of the recruitment to the trial.

Please add a statement to confirm that all authors have viewed and agreed to the submission

All authors have collaborated in this submission

This information must also be inserted into your manuscript under the acknowledgements section prior to the References.

INTERNATIONAL JOURNAL OF ORAL & MAXILLOFACIAL SURGERY**CONFIRMATION OF AUTHORSHIP FORM**

Title of Submission: Using the PCI in the identification of fatigue following treatment for head and neck cancer

Contributing Authors :-**Author:** (surname and initials)**Signature (Mandatory)**

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2. Semple C



3. Humphris GM



4. Lowe D



5. Kanatas A



"I warrant that all the authors listed above have made a significant contribution to this manuscript and have agreed to its submission to the IJOMS".

Signed (corresponding author)**Name and Title of Corresponding Author:** Professor S N Rogers

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Table 1 : Selection of the PCI 'fatigue' item, by casemix

		%	PCI FATIGUE SELECTED Patients	P value**
	Total patients	29	40/140	
Hospital	Aintree	27	22/82	0.70
	Leeds	31	18/58	
Days from diagnosis to first clinic (TERTILES)	≤144	19	9/48	0.16
	125-227	36	16/45	
	≥228	32	15/47	
Days from end of treatment to first clinic (TERTILES)	≤79	29	14/49	0.84
	80-138	26	12/46	
	≥139	31	14/45	
Duration of consultation (minutes) TERTILES	≤8 mins	11	4/37	0.005
	9-12 mins	29	14/49	
	≥13 mins	42	21/50	
Gender	Female	37	18/49	0.12
	Male	24	22/91	
Age	<55	38	11/29	0.48
	55-64	26	16/52	
	65-74	31	10/32	
	≥75	18	3/17	
Tumour site:	Oral cavity	18	10/55	0.10
	Oropharynx	36	15/42	
	Larynx	30	9/30	
	Other	46	6/13	
Overall clinical stage	Advanced 3-4	36	30/84	0.02
	Early 1-2	18	10/56	
Primary treatment*:	S only	13	6/46	0.004
	S only & FF	-	0/7	
	RT or RT/CT only	39	15/38	
	S & (RT or RT/CT)	45	14/31	
	S & (RT or RT/CT) & FF	28	5/18	
WHO comorbidity	0	32	28/88	0.55
	1	25	7/28	
	2-4	21	5/24	
ACE27 comorbidity	None	32	23/71	0.25
	Mild	24	10/41	
	Moderate	20	5/25	
	Severe	67	2/3	
Living situation	Alone in house/flat	17	5/29	0.17
	With others in house/flat	32	35/111	
Working	Yes	29	14/48	>0.99
	No	29	25/86	
Financial benefits	Yes	31	15/49	0.69
	No	27	21/78	
Smoking habit	Current	19	3/16	0.48
	Former	27	22/81	
	Never	34	13/38	
Alcohol habit	Current	24	24/100	0.10
	Former	37	11/30	
	Never	60	3/5	
IMD 2019 quintile	1=least deprived	50	8/16	0.32
	2	28	8/29	
	3	18	4/22	
	4	24	4/17	
	5=most deprived	29	16/56	

* Surgery (S), RadioTherapy (RT), ChemoTherapy (CT), Free Flap transfer (FF)

** Fishers Exact test

Table 2: Selection of the PCI 'fatigue' item, by QOL measures

		PCI FATIGUE SELECTED		P value**
		%	Patients	
All patients		29	40/140	
UWQOL Overall Quality of life	Outstanding/ Very good	11	5/47	0.002
	Good	31	15/48	
	Fair	41	14/34	
	Very Poor / Poor	55	6/11	
Distress thermometer (DT)	Zero	11	4/36	0.02
	1-3	26	10/38	
	4-5	39	13/33	
	6-10	39	13/33	
UWQOL social-emotional subscale	<60	52	13/25	<0.001
	60-79	40	21/53	
	80-100	10	6/62	
UWQOL physical function subscale	<60	39	16/41	0.001
	60-79	36	20/55	
	80-100	9	4/44	
UWQOL items				
<u>Social-emotional subscale</u>				
• Pain	Best possible response	17	9/53	0.05
	Somewhere in-between	33	16/48	
	Dysfunction	38	15/39	
• Activity	Best possible response	7	3/46	<0.001
	Somewhere in-between	36	29/80	
	Dysfunction	57	8/14	
• Recreation	Best possible response	11	7/61	<0.001
	Somewhere in-between	39	28/71	
	Dysfunction	63	5/8	
• Shoulder	Best possible response	26	22/85	0.64
	Somewhere in-between	34	14/41	
	Dysfunction	29	4/14	
• Mood	Best possible response	8	4/48	<0.001
	Somewhere in-between	41	31/75	
	Dysfunction	29	5/17	
• Anxiety	Best possible response	15	7/47	0.003
	Somewhere in-between	29	20/69	
	Dysfunction	54	13/24	
<u>Physical function subscale</u>				
• Appearance	Best possible response	21	9/43	0.41
	Somewhere in-between	31	27/86	
	Dysfunction	36	4/11	
• Swallowing	Best possible response	14	7/50	0.01
	Somewhere in-between	36	26/73	
	Dysfunction	41	7/17	
• Chewing	Best possible response	19	11/57	0.11
	Somewhere in-between	36	23/64	
	Dysfunction	32	6/19	
• Speech	Best possible response	28	18/64	0.68
	Somewhere in-between	27	18/66	
	Dysfunction	40	4/10	
• Taste	Best possible response	12	5/41	0.008
	Somewhere in-between	32	23/72	
	Dysfunction	44	12/27	
• Saliva	Best possible response	12	5/41	0.001
	Somewhere in-between	23	11/47	
	Dysfunction	46	24/52	
Other items:				
• Intimacy	Best possible response	25	27/110	0.04
	Somewhere in-between	50	12/24	
	Dvsfunction	17	1/6	

• Fear of recurrence*	0 or 25	50	8/16	0.01
	50	40	17/43	
	75	21	13/62	
	100	11	2/19	
EQ-5D				
Mobility (walking about)	No problems	25	24/96	0.36
	Slight problems	37	7/19	
	Moderate/severe/unable	36	9/25	
Self-care (washing or dressing myself)	No problems	24	27/113	0.03
	Slight problems	55	6/11	
	Moderate/severe/unable	44	7/16	
Usual activities	No problems	16	12/76	<0.001
	Slight problems	31	11/35	
	Moderate/severe/unable	59	17/29	
Pain (or discomfort)	No pain or discomfort	15	8/54	0.01
	Slight pain or discomfort	33	14/42	
	Moderate/severe/extreme	41	18/44	
Anxiety/depression	Not anxious or depressed	21	14/67	0.01
	Slightly anxious or depressed	29	17/58	
	Moderate/severe/extreme	60	9/15	
EQ-5D-5L TTO crosswalk values (TERTILES)	≤.6950	45	17/38	0.001
	.6951-.8370	31	19/61	
	≥.8371	10	4/41	
EQ5D Visual analogue scale (VAS) TERTILES	≤69	46	21/46	<0.001
	70-81	32	14/44	
	≥82	10	5/50	

*(0) I am fearful all the time that my cancer might return and I struggle with this n=2, (25) I get a lot of fears of recurrence and these can really preoccupy my thoughts n=14, (50) I am sometimes having fearful thoughts but I can usually manage these (75) I have a little fear with occasional thoughts but they don't really bother me (100) I have no fear of recurrence

** Fishers Exact test

Table 3: Selection of the PCI 'fatigue' item and other PCI data

		PCI FATIGUE SELECTED		P value
		%	Patients	
Patients		29	40/140	
No of PCI selected: overall	<5	2	1/57	<0.001
	5-9	30	15/50	
	10-14	65	13/20	
	≥15	85	11/13	
PCI items selected by domain:				
Physical function	<5	8	6/75	<0.001
	5-9	37	16/43	
	≥10	82	18/22	
Cancer treatment	None	24	24/98	0.11
	≥1	38	16/42	
Social care & social wellbeing	None	23	25/109	0.01
	≥1	48	15/31	
Psychological, emotional wellbeing/spiritual	None	11	7/65	<0.001
	1	27	12/44	
	≥2	68	21/31	
No. of Health professionals selected	None	23	17/75	0.05
	≥1	35	23/65	
Other PCI items selected by at least 20% of patients overall	Dry mouth	40	27/68	0.005
	Fear of cancer coming back	48	23/48	<0.001
	Dental health/Teeth	44	21/48	0.006
	Chewing/eating	43	20/46	0.009
	Salivation	48	22/46	0.001
	Swallowing	51	20/39	<0.001
	Taste	42	16/38	0.04
	Sore mouth	45	15/33	0.03
	Mucus	48	16/33	0.007
	Shoulder	45	14/31	0.03
	Pain in the head and neck	57	17/30	<0.001
	Cancer treatment	39	11/28	0.17
Other PCI items*	Activity	50	3/6	0.35
	Appetite	52	14/27	0.004
	Bowel habit	50	6/12	0.10
	Breathing	67	6/9	0.02
	Energy levels	60	15/25	<0.001
	Indigestion	50	3/6	0.35
	Mobility	70	7/10	0.006
	Nausea	83	5/6	0.007
	Pain elsewhere	54	7/13	0.05
	Sleeping	81	13/16	<0.001
	Vomiting	80	4/5	0.02
	Financial benefits	67	4/6	0.06
	Speech/voice/being understood	60	9/15	0.01
	Anxiety	56	9/16	0.02
	Depression	75	6/8	0.007
	Memory	60	6/10	0.03
	Mood	83	5/6	0.007
	Self-esteem	67	4/6	0.06
	Personality & temperament	60	3/5	0.14
	Other Health professionals*	Oral rehab team	57	4/7
Physiotherapy		63	5/8	0.04
Audiologist		50	4/8	0.23

*when these items were selected then Fatigue was selected in at least 50% of the patients. Denominators under 5 were omitted

International Journal of Oral & Maxillofacial Surgery

10th September 2020

Editor-in-Chief

Professor Nabil Samman

Dear Nabil,

Thank you for the feedback with respect the submission entitled '**Using the PCI in the identification of fatigue following treatment for head and neck cancer**'

Ms. Ref. No.: IJOMS-D-20-01101.

Section Editor: It is an interesting paper, of interest to our readers and adds new knowledge to the literature, that we can definitely publish.

Thank you

i have only two suggestions

Line 41-42 Should write out in full the first time abbreviations are used as not all readers are familiar with these QoL instruments i.e UW-QoLv4 (University of Washington Quality of Life) and EQ-5D-5L (EuroQol Group 5 dimensions?)

Thank you. The abbreviations were there to save word space. The abstract has been amended to include this recommendation but did involve a few other minor changes in order to keep to the 200-word limit.

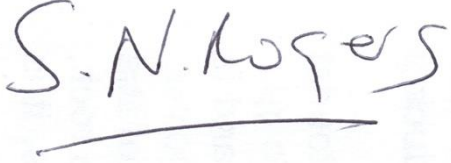
Line 220 Given the association of hypothyroidism with radiation therapy does this account for the higher % of fatigue in these patients. Do the authors know how many of these patients had hypothyroidism and was there a significant correlation with radiation? Should these patients all have a thyroid function test screen?

This is a good point but unfortunately, we don't routinely measure for hypothyroidism in our head and neck cancer practice. These sentences have been added to the discussion

In our HNC follow-up strategy there is no protocol for routinely checking for anaemia or hypothyroidism. Based on the PCI response and other patient reported outcomes measures that ask about activity, recreation or fatigue, it would be possible to build in an alert such that low scores in these domains triggers the suggestion to the clinician to check the full blood count and thyroxine function test.

Thank you so much for your consideration.

Yours sincerely

A handwritten signature in dark ink that reads "S. N. Rogers". The signature is written in a cursive style with a horizontal line underneath the name.

Simon N Rogers

On behalf of the other co-authors:

Dr Cherith J Semple Institute of Nursing and Health Research, Ulster University.

Professor Gerald M Humphris School of Medicine, St Andrews University.

Mr Derek Lowe Medical Statistician, Director, Astraglobe Ltd.

Professor Anastasios Kanatas, Leeds Teaching Hospitals and St James Institute of Oncology.

Using the PCI in the identification of fatigue following treatment for head and neck cancer

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Trial registration: 32,382. Clinical Trials Identifier, NCT03086629.

Keywords: Fatigue; head and neck cancer; intervention; prompt list; health related quality of life; Patient Concerns Inventory

Abstract

Fatigue has a profound impact on health-related quality of life (HRQOL) and the aim of this study is to describe the clinical characteristics and HRQOL for head and neck cancer patients who raise the issue of fatigue on the Patient Concerns Inventory (PCI), at their review consultation. Eight consultants were randomised to use the PCI as part of a cluster-controlled trial. Patients also completed the UW-QoLv4 (University of Washington Quality of Life), EQ-5D-5L (EuroQol Group) and Distress Thermometer. There were 140 patients who attended clinics at a median (IQR) of 108 (70-165) days after the end of treatment. The PCI item 'fatigue' was the 6th most commonly selected, by 29% (40). Those with advanced tumours were more likely (36% 30/83 Vs 18% 10/56, $p=0.02$) to have selected the item, as were those treated with radiotherapy +/- chemotherapy (39% 34/87 Vs 11% 6/53, $p<0.001$). The PCI fatigue group reported significantly worse overall QOL, social-emotional and physical function composite scores, distress thermometer, and EQ-5D. PCI-fatigue was common in those with sleeping, nausea, mood, depression, mobility, breathing and energy level concerns. In conclusion, given the problems associated with fatigue, it is appropriate to screen and seek interventions that might help patient address this.

Introduction

Head and neck cancer (HNC) survivors commonly experience cancer-related fatigue (CRF) and this relates to disease, treatment and individual patient characteristics¹. Moderate and severe fatigue was reported in one fifth of HNC survivors². Cancer-related fatigue compromises survival rates and negatively impacts on activities of daily living (ADLs)³. Fatigue is a barrier to getting back to work⁴. Although the precise mechanism for CRF experienced by HNC survivors is unclear and is probably multi-factorial, radiation to the central nervous system has been implicated, particularly the treatment dose to the brainstem and medulla⁵. Neuroinflammation can also contribute to chronic systemic symptoms such as fatigue, sleep disturbance, chronic widespread pain, mood disorders, neuropsychiatric symptoms, and temperature dysregulation⁶. Patients receiving intensity-modulated radiation therapy (IMRT) seem to have high rates of fatigue, and further research on how inflammation contributes to fatigue is needed⁷. Depression and fatigue symptoms are interlinked and correlate to poor health-related quality of life outcomes (HRQOL)⁸. Evaluation throughout the treatment is important⁹ and fatigue is at its worse around the 6th week of radiation treatment, and slowly improves thereafter¹⁰. Various clinical characteristics associated with worse fatigue have been suggested for example, younger age, previous radiation, depression, and other symptoms such as poor sleep, reduced social activity and cognitive dysfunction^{11, 12}. In a study which utilised the Modified Brief Fatigue Inventory (MBFI), comorbidity and cancer stage were also implicated¹³. It has been suggested that both fatigue and depression should be periodically assessed as both are late effects¹⁴. It is already appreciated that fatigue is an issue that patients wish to talk about in their consultations but little is known about the patient characteristic. Previous reports using the Patient Concerns Inventory (PCI) following HNC treatment has placed fatigue as the 5th most frequent item of the 56 items, being common in early and late stage disease across all sites (oral, oropharyngeal, laryngeal and other)¹⁵.

The aim of this study is to describe the clinical characteristics and HRQOL for those HNC patients who raise the issue of fatigue as something they wish to discuss in their review consultation. Understanding the complexity of CRF as it relates to clinical characteristics and using this knowledge to guide the development of targeted, individualised interventions is critical for reducing the burden of this symptom for HNC survivors.

Method

The methods have been described previously¹⁶. Briefly, the data is from a pragmatic cluster-controlled trial conducted at two UK Cancer Centres, namely Aintree and Leeds. Fifteen consultants (the clustering factor) were randomised, eight to ‘using’ and seven to ‘not using’ an intervention incorporating the PCI prompt list at all their trial clinics. Eligible patients were treated curatively for primary or secondary HNC, and included all sites, stages of disease and treatments. Patients treated palliatively or with recurrence, history of cognitive impairment, psychoses or dementia were excluded. The focus of this paper is to report results from the first ‘baseline’ post-treatment consultation of only the PCI intervention group patients. The PCI prompt list consists of 56 clinical items¹⁷ which patients selected from, at clinic, before seeing their consultant. The patient generated list guides the outpatient consultation and it covers a range of symptoms and potential problems patients may face after treatment. The item relating to fatigue is described as “fatigue/tiredness” on the prompt list, and which in this paper we will simply refer to as “fatigue”. Patients were also asked to select from a list of 18 types of health professional, who they would ‘like to see or be referred to’. Previous work [18] grouped PCI items into four domains: Physical and Functional well-being (29 items), Treatment-related (4 items), Social care/Social well-being (9 items) Psychological and Emotional well-being/Spiritual (14 items).

Clinical and demographic data were collected by a baseline questionnaire or by extraction from electronic records. HRQOL and PCI data were completed electronically (iPAD). HRQOL data included UW-QOLv4¹⁹, Distress thermometer²⁰ and EQ-5D-5L²¹. The UW-QOLv4 questionnaire consists of 12 single question domains, with between 3 and 5 response options scaled evenly from 0 (worst) to 100 (best) according to response hierarchy (Rogers 2002). It also contains a question about overall QOL in which patients are asked to consider not only physical and mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life. Subsequent analysis has led to the development of subscale composite scores²² and domain algorithms to screen for significant problems/dysfunction²³.

The statistical analysis focussed on variables associated with selection of the fatigue item from the PCI prompt list. We considered patient and clinical casemix variables and also a wide range of HRQOL measures. Fishers Exact test was used to compare patient groups regarding selection of the fatigue item. Spearman’s correlation coefficient (r_s) was used to

assess association between the UWQOL activities domain response options and those of the EQ5D-5L usual activities domain. The PCI trial has ethical approval from North West - Liverpool Central Research Ethics Committee REC reference: IRAS 16/NW/0465, Project ID: 189554. It also has approval from the Health Research Authority (HRA). The Research and Development Department at Aintree University Hospital NHS Trust (AUH) is coordinating the trial and AUH is the sponsor for the trial.

Results

Patients recruited to the trial and having baseline data were first discussed at multidisciplinary team (MDT) meetings between January 2017 and December 2018, with first trial clinics between April 2017 and October 2019. Of 288 patients in the trial, 140 were in the PCI intervention group. Clinics were a median (IQR) of 189 (120-255) days after diagnosis and 108 (70-165) after the end of treatment. Characteristics of the 140 PCI group patients can be determined from Table 1.

The mean number of items selected by the 140 PCI patients for discussion in their consultation was 6.60, median (IQR) 5 (2-9), range 0 to 28 with 15 or more items selected by 9% (13). The PCI item 'fatigue' was the 6th most commonly selected, by 29% (40), coming after 'dry mouth' (49%, 68), 'fear of cancer coming back' (34%, 48), 'dental health/teeth' (34%, 48), 'chewing/eating' (33%, 46) and 'salivation' (33%, 46). The longer the consultation the more likely the fatigue item had been selected for discussion (Table 1). Those with advanced tumours were more likely (36% 30/83 Vs 18% 10/56, $p=0.02$) to have selected the fatigue item, as were those having received radiotherapy +/- chemotherapy (39% 34/87 Vs 11% 6/53, $p<0.001$).

Selection of the 'fatigue' item was associated with most of the measured HRQOL variables (Table 2). In particular, there was a clear gradient of selection with overall QOL, ranging from 11% selecting fatigue in patients reporting very good or outstanding QOL to 55% if reporting very poor or poor overall QOL. Clear gradients were seen also regarding the distress thermometer score, the EQ-5D visual analogue scale and EQ-5D TTO crosswalk values. Regarding the UWQOL, this was also evident for both the social-emotional and physical function composite scores. Strong associations were seen with the UWQOL activity domain, the EQ-5D usual activities domain and also with UWQOL recreation, mood, anxiety, saliva and taste domains.

The UWQOL activities domain has five response options, namely, (1) I am usually in bed or chair and don't leave home, (2) I don't go out because I don't have the strength, (3) I am often tired and have slowed down my activities although I still get out (4) There are times when I can't keep up my old pace, but not often and (5) I am as active as I have ever been. Seven patients responded to option 1 or option 2 and 86% (6/7) of these selected fatigue for discussion in their consultation, as did 52% (27/52) for option 3, 11% (4/35) for option 4 and 7% (3/46) for option 5. The EQ5D usual activities domain also has five response options (1) I have no problems doing my usual activities, (2) I have slight problems doing my usual activities, (3) I have moderate problems doing my usual activities, (4) I have severe problems doing my usual activities and (5) I am unable to do my usual activities. Six patients selected option 4 or option 5 and 83% (5/6) selected fatigue, as did 52% (12/23) for option 3, 31% (11/35) for option 2 and 16% (12/76) for option 1. Spearman correlation between the two 5-point measures was $R_s = -0.55$, $p < 0.001$.

Quite clearly the greater the number of PCI items selected the more likely was this number to include fatigue (Table 3), and the same could be said for each of the four PCI domains, and also if health professionals were also selected. Only 2 of the 56 PCI items were not selected by these patients and 4 had very small denominators of under 5 patients; for 48 of the other 50 items the selection of fatigue was higher when that item was selected than when that item was not selected. When sleeping was selected fatigue was also selected in 81% (13/16); higher fatigue selection rates of around 50% and higher were also seen for many variables (Table 3) including nausea (83%, 5/6), mood (83%, 5/6), depression (75%, 6/8), mobility (70%, 7/10), breathing (67%, 6/9) and energy levels (60%, 15/25).

Discussion

CRF following the diagnosis of HNC tends to be under-reported, potentially persistent and of substantial significance to patients, impacting on HRQOL and survival. There are many different aspects including physical, pain, psychological and social factors which contribute to patients' perceived levels of CRF². The PCI is a well reported prompt list^{15,16,18} and as well as allowing a wide range of factors to be considered it is also an holistic approach to delivering patient-centred care. It can be integrated into routine clinics^{24,25}. The specific issue of fatigue reported by the PCI has not previously been assessed in detail, and this novel data has been taken from a cluster randomisation trial involving eight different consultants. The variety of

consultants across two centres, set within the context of routine follow-up consultations means that the findings of this study are pertinent to current practice. The sample comprises of the range of HNC sites managed by head and neck oncology surgeons. The focus of the assessment is around three to six months following completion of treatment. Nautiyal et al¹ reported a dramatic improvement in fatigue levels across the first 3 months post-treatment, followed by a slow improvement over the remainder of the first year, but with higher fatigue levels than those of healthy individuals. Although a fatigue specific questionnaire such as the Modified Brief Fatigue Inventory (MBFI) was not used, the degree of fatigue experienced by the patient will be reflected by the activity and recreation domains of the UW-QOL^{26,27}. There are other factors that might contribute to fatigue such as HPV status as this and inflammation were found to be independent predictors of fatigue over time²⁸. As the PCI can be used at consultations, the prompt of fatigue affords an opportunity for further exploration, plus provision of informal advice and support for both patients and their caregivers. Other unmet needs self-report measures²⁹ or Vanderbilt Head and Neck Symptom survey³⁰ might fulfil a similar purpose.

Over a quarter of the patients wished to talk about fatigue at their consultations. Fatigue was more common when primary treatment related to radiotherapy +/- chemotherapy rather than surgery alone, and expressed by patients with advanced stage. In this sample there was little obvious difference in the frequency that patients wished to talk about fatigue by age, gender, comorbidity and socio-economic group. Those selecting fatigue reported significantly worse QOL, lower scores in the UW-QOL domains apart from appearance, chewing, shoulder and speech. In addition, patients reported worse intimacy, fear of recurrence, distress, and were more likely to report moderate to extreme problems in usual activities (EQ-5D). Fatigue on the PCI was combined with other issues such as appetite, energy levels, sleeping, depression and mood and this reflects the complex nature of inter-related symptoms.

In those patients with CRF, anaemia or hypothyroidism, if present should be corrected and pain control attended to. In our HNC follow-up strategy there is no protocol for routinely checking for anaemia or hypothyroidism. Based on the PCI response and other patient reported outcomes measures that ask about activity, recreation or fatigue, it would be possible to build in an alert such that low scores in these domains triggers the suggestion to the clinician to check the full blood count and thyroxine function test.

It is possible to consider additional interventions. Even though patients might feel too tired to exercise and the symptom persists, there is evidence that if appropriately graded they can

complete an exercise programme, with notable benefits. HNC patients can find it a challenge to exercise²⁷ and prescription should be individually tailored to patient characteristics³¹. A clinic-supported, 12-week progressive strength-training exercise intervention for HNC patients was associated with significant improvements in physical functioning outcomes and improved management of tiredness and fatigue³². Physical exercise interventions demonstrated improvements in physical function, muscular endurance, range of motion, overall quality of life, and showed reductions in pain, and fatigue³³. Progressive resistance training in cachectic HNC patients during radiotherapy seems to be safe and feasible and may have beneficial effects of general fatigue and quality of life³⁴. A home-based personalized behavioural physical activity intervention with fitness graded motion exergames (PAfitME) has been shown to be feasible and acceptable with improvement in CRF, ADL dependence, cardiorespiratory fitness, balance, muscle strength, and shoulder forward flexion³. Another aspect that might make a positive impact is optimisation of nutrition. HNC patients can be malnourished at the time of diagnosis and the side-effects of treatment can exacerbate this through detrimental effects on loss of taste, mucositis, xerostomia, anorexia, nausea and vomiting. Nutritional advice and use of supplements should be used to increase dietary intake and to prevent therapy-associated weight loss³⁵. In nasopharyngeal carcinoma patients, nutrition counselling combined with head and neck rehabilitation exercises greatly reduced fatigue three months after intensity-modulated radiotherapy (IMRT)³⁶. Poor sleep quality is another factor that is related to fatigue and if obstructive sleep apnoea is a contributing factor to sleep disturbance this needs to be addressed³⁷. Interventions aimed at the interaction between the emotional aspects of fatigue and HNC outcomes are appropriate and can have long-term beneficial effects³⁸. In a study of fatigability, depression, and self-esteem among HNC patients, Joseph et al reported that over two thirds of patients had fatigue and a larger proportion suffered from depression¹⁴. The role of social support is vital as it improves emotional adaptation and reduces depressive symptoms. Also, an appreciation of the difficulties involved in social activities exacerbated by a sense of fatigue can result in further social isolation⁸. As the issue of CRF tends to be multi-factorial further research is needed using complex intervention methodology.

In conclusion, a significant proportion of HNC patients following treatment wish to discuss the issue of fatigue during their out-patient consultation. Fatigue is associated with poor outcomes. As fatigue can be a patient concern over an extended period of time, the PCI

prompt list approach could facilitate the discussion during follow-up and allow for further investigation and targeted onward referral based on the aetiology of the fatigue.

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Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1 : Selection of the PCI 'fatigue' item, by casemix

		%	PCI FATIGUE SELECTED Patients	P value**
	Total patients	29	40/140	
Hospital	Aintree	27	22/82	0.70
	Leeds	31	18/58	
Days from diagnosis to first clinic (TERTILES)	≤144	19	9/48	0.16
	125-227	36	16/45	
	≥228	32	15/47	
Days from end of treatment to first clinic (TERTILES)	≤79	29	14/49	0.84
	80-138	26	12/46	
	≥139	31	14/45	
Duration of consultation (minutes) TERTILES	≤8 mins	11	4/37	0.005
	9-12 mins	29	14/49	
	≥13 mins	42	21/50	
Gender	Female	37	18/49	0.12
	Male	24	22/91	
Age	<55	38	11/29	0.48
	55-64	26	16/52	
	65-74	31	10/32	
	≥75	18	3/17	
Tumour site:	Oral cavity	18	10/55	0.10
	Oropharynx	36	15/42	
	Larynx	30	9/30	
	Other	46	6/13	
Overall clinical stage	Advanced 3-4	36	30/84	0.02
	Early 1-2	18	10/56	
Primary treatment*:	S only	13	6/46	0.004
	S only & FF	-	0/7	
	RT or RT/CT only	39	15/38	
	S & (RT or RT/CT)	45	14/31	
	S & (RT or RT/CT) & FF	28	5/18	
WHO comorbidity	0	32	28/88	0.55
	1	25	7/28	
	2-4	21	5/24	
ACE27 comorbidity	None	32	23/71	0.25
	Mild	24	10/41	
	Moderate	20	5/25	
	Severe	67	2/3	
Living situation	Alone in house/flat	17	5/29	0.17
	With others in house/flat	32	35/111	
Working	Yes	29	14/48	>0.99
	No	29	25/86	
Financial benefits	Yes	31	15/49	0.69
	No	27	21/78	
Smoking habit	Current	19	3/16	0.48
	Former	27	22/81	
	Never	34	13/38	
Alcohol habit	Current	24	24/100	0.10
	Former	37	11/30	
	Never	60	3/5	
IMD 2019 quintile	1=least deprived	50	8/16	0.32
	2	28	8/29	
	3	18	4/22	
	4	24	4/17	
	5=most deprived	29	16/56	

* Surgery (S), RadioTherapy (RT), ChemoTherapy (CT), Free Flap transfer (FF)

** Fishers Exact test

Table 2: Selection of the PCI 'fatigue' item, by QOL measures

		PCI FATIGUE SELECTED		P value**
		%	Patients	
All patients		29	40/140	
UWQOL Overall Quality of life	Outstanding/ Very good	11	5/47	0.002
	Good	31	15/48	
	Fair	41	14/34	
	Very Poor / Poor	55	6/11	
Distress thermometer (DT)	Zero	11	4/36	0.02
	1-3	26	10/38	
	4-5	39	13/33	
	6-10	39	13/33	
UWQOL social-emotional subscale	<60	52	13/25	<0.001
	60-79	40	21/53	
	80-100	10	6/62	
UWQOL physical function subscale	<60	39	16/41	0.001
	60-79	36	20/55	
	80-100	9	4/44	
UWQOL items				
<u>Social-emotional subscale</u>				
• Pain	Best possible response	17	9/53	0.05
	Somewhere in-between	33	16/48	
	Dysfunction	38	15/39	
• Activity	Best possible response	7	3/46	<0.001
	Somewhere in-between	36	29/80	
	Dysfunction	57	8/14	
• Recreation	Best possible response	11	7/61	<0.001
	Somewhere in-between	39	28/71	
	Dysfunction	63	5/8	
• Shoulder	Best possible response	26	22/85	0.64
	Somewhere in-between	34	14/41	
	Dysfunction	29	4/14	
• Mood	Best possible response	8	4/48	<0.001
	Somewhere in-between	41	31/75	
	Dysfunction	29	5/17	
• Anxiety	Best possible response	15	7/47	0.003
	Somewhere in-between	29	20/69	
	Dysfunction	54	13/24	
<u>Physical function subscale</u>				
• Appearance	Best possible response	21	9/43	0.41
	Somewhere in-between	31	27/86	
	Dysfunction	36	4/11	
• Swallowing	Best possible response	14	7/50	0.01
	Somewhere in-between	36	26/73	
	Dysfunction	41	7/17	
• Chewing	Best possible response	19	11/57	0.11
	Somewhere in-between	36	23/64	
	Dysfunction	32	6/19	
• Speech	Best possible response	28	18/64	0.68
	Somewhere in-between	27	18/66	
	Dysfunction	40	4/10	
• Taste	Best possible response	12	5/41	0.008
	Somewhere in-between	32	23/72	
	Dysfunction	44	12/27	
• Saliva	Best possible response	12	5/41	0.001
	Somewhere in-between	23	11/47	
	Dysfunction	46	24/52	
Other items:				
• Intimacy	Best possible response	25	27/110	0.04
	Somewhere in-between	50	12/24	
	Dysfunction	17	1/6	

• Fear of recurrence*	0 or 25	50	8/16	0.01
	50	40	17/43	
	75	21	13/62	
	100	11	2/19	
EQ-5D				
Mobility (walking about)	No problems	25	24/96	0.36
	Slight problems	37	7/19	
	Moderate/severe/unable	36	9/25	
Self-care (washing or dressing myself)	No problems	24	27/113	0.03
	Slight problems	55	6/11	
	Moderate/severe/unable	44	7/16	
Usual activities	No problems	16	12/76	<0.001
	Slight problems	31	11/35	
	Moderate/severe/unable	59	17/29	
Pain (or discomfort)	No pain or discomfort	15	8/54	0.01
	Slight pain or discomfort	33	14/42	
	Moderate/severe/extreme	41	18/44	
Anxiety/depression	Not anxious or depressed	21	14/67	0.01
	Slightly anxious or depressed	29	17/58	
	Moderate/severe/extreme	60	9/15	
EQ-5D-5L TTO crosswalk values (TERTILES)	≤.6950	45	17/38	0.001
	.6951-.8370	31	19/61	
	≥.8371	10	4/41	
EQ5D Visual analogue scale (VAS) TERTILES	≤69	46	21/46	<0.001
	70-81	32	14/44	
	≥82	10	5/50	

*(0) I am fearful all the time that my cancer might return and I struggle with this n=2, (25) I get a lot of fears of recurrence and these can really preoccupy my thoughts n=14, (50) I am sometimes having fearful thoughts but I can usually manage these (75) I have a little fear with occasional thoughts but they don't really bother me (100) I have no fear of recurrence

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Table 3: Selection of the PCI 'fatigue' item and other PCI data

		PCI FATIGUE SELECTED		P value
		%	Patients	
Patients		29	40/140	
No of PCI selected: overall	<5	2	1/57	<0.001
	5-9	30	15/50	
	10-14	65	13/20	
	≥15	85	11/13	
PCI items selected by domain:				
Physical function	<5	8	6/75	<0.001
	5-9	37	16/43	
	≥10	82	18/22	
Cancer treatment	None	24	24/98	0.11
	≥1	38	16/42	
Social care & social wellbeing	None	23	25/109	0.01
	≥1	48	15/31	
Psychological, emotional wellbeing/spiritual	None	11	7/65	<0.001
	1	27	12/44	
	≥2	68	21/31	
No. of Health professionals selected	None	23	17/75	0.05
	≥1	35	23/65	
Other PCI items selected by at least 20% of patients overall	Dry mouth	40	27/68	0.005
	Fear of cancer coming back	48	23/48	<0.001
	Dental health/Teeth	44	21/48	0.006
	Chewing/eating	43	20/46	0.009
	Salivation	48	22/46	0.001
	Swallowing	51	20/39	<0.001
	Taste	42	16/38	0.04
	Sore mouth	45	15/33	0.03
	Mucus	48	16/33	0.007
	Shoulder	45	14/31	0.03
	Pain in the head and neck	57	17/30	<0.001
	Cancer treatment	39	11/28	0.17
Other PCI items*	Activity	50	3/6	0.35
	Appetite	52	14/27	0.004
	Bowel habit	50	6/12	0.10
	Breathing	67	6/9	0.02
	Energy levels	60	15/25	<0.001
	Indigestion	50	3/6	0.35
	Mobility	70	7/10	0.006
	Nausea	83	5/6	0.007
	Pain elsewhere	54	7/13	0.05
	Sleeping	81	13/16	<0.001
	Vomiting	80	4/5	0.02
	Financial benefits	67	4/6	0.06
	Speech/voice/being understood	60	9/15	0.01
	Anxiety	56	9/16	0.02
	Depression	75	6/8	0.007
	Memory	60	6/10	0.03
	Mood	83	5/6	0.007
	Self-esteem	67	4/6	0.06
	Personality & temperament	60	3/5	0.14
	Other Health professionals*	Oral rehab team	57	4/7
Physiotherapy		63	5/8	0.04
Audiologist		50	4/8	0.23

*when these items were selected then Fatigue was selected in at least 50% of the patients. Denominators under 5 were omitted



Health Research Authority

North West - Liverpool Central Research Ethics Committee

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Manchester
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Telephone: 020 71048008

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 July 2016

Prof Simon Rogers
Aintree University Hospital
Longmoor Lane
Liverpool
L7 9AL

Dear Prof Rogers

Study title:	Improving quality of life through the routine use of the Patient Concerns Inventory for head and neck cancer patients (PCI-QOL)
REC reference:	16/NW/0465
IRAS project ID:	189554

The Research Ethics Committee reviewed the above application at the meeting held on 06 July 2016. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Mrs Carol Ebenezer, nrescommittee.northwest-liverpoolcentral@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

- the Committee would like to see the Participant Information Sheet revised to
 - i) include a further paragraph “What if something goes wrong?” and state that if something goes wrong the normal NHS compensation procedures would apply
 - ii) under “What are the side effects and risks?” add the words “There are no perceived risks to taking part but it might inconvenience you by prolonging your clinic time” and omit the current wording “This might prolong your clinic time”
- b. the Committee would like to see the PCI revised to replace NHS number with unique identifier
- c. the Committee would like to know for how long the data will be kept

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation’s role in the study is limited to identifying and referring potential participants to research sites (“participant identification centre”), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

The Chair welcomed you to the REC and thanked you for attending to discuss the study. The Committee told you that this was a really good and worthwhile study.

Care and protection of research participants; respect for potential and enrolled participants' welfare and dignity

The Committee pointed out that there was a discrepancy in the stated time for storage of data at the end of the study and asked you for how long it would be kept and how it would be destroyed.

You stated that you would check with the NHIR and advise the Committee.

Informed consent process and the adequacy and completeness of participant information

The Committee advised that some minor changes to the Participant Information Sheet were required (as listed on the decision below) and that these would be included in the decision letter.

Suitability of supporting information

The Committee asked that the PCI be changed to omit the NHS number and include, instead, the unique identifier.

You agreed to this and stated that the NHS number was on the form because it was currently used in clinical practice.

You had no questions for the Committee.

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
IRAS Application Form [IRAS_Form_26052016]		26 May 2016
Letter from funder [Funder Letter]		
Letter from sponsor [Sponsor Approval Letter]		
Non-validated questionnaire [Distress Thermometer]	1	26 May 2016
Non-validated questionnaire [EQ-5D-3L Questionnaire]	1	26 May 2016
Non-validated questionnaire [Preconsultation Questionnaire]	1	26 May 2016
Non-validated questionnaire [UW-QOL Questionnaire]	4	26 May 2016
Non-validated questionnaire [CRSI-PCI-QoL]	1	26 May 2016
Other [email regarding Independent Review]		08 June 2016
Participant consent form	1	26 May 2016
Participant information sheet (PIS) [PIS V1 26.5.16]	1	26 May 2016
Research protocol or project proposal	1	26 May 2016
Summary CV for Chief Investigator (CI) [Prof Simon Rogers]		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: <http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

16/NW/0465

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

A handwritten signature in black ink, appearing to read 'J. Brake', is written over a printed name and title.

Mrs Julie Brake
Chair

E-mail: nrescommittee.northwest-liverpoolcentral@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Mrs Michelle Mossa, University Hospital Aintree NHS Foundation Trust

North West - Liverpool Central Research Ethics Committee

Attendance at Committee meeting on 06 July 2016

Committee Members:

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Ms Zainab Ahmed	REC Assistant	No	
Mr Simon Alford	Research Manager	Yes	
Mrs Julie Brake	Specialist Diabetes Nurse / Chair	Yes	
Mr James Burns	Retired Lay Member	Yes	
Professor Murthy Burra	Consultant Anaesthetist	No	
Mrs Hannah Chambers	Lay Member	Yes	
Mrs Sue Fitzpatrick	Director	Yes	
Mr Derek Hollingsbee	Pharmacist	Yes	
Mr Frank Killen	Retired Engineer	No	
Miss Karen Knowles	Biomedical Scientist	Yes	
Mr Fotios Polydoros	Statistician	No	
Ms Jennifer Preston	Patient and Public Involvement Manager	No	
Dr Lyvonne Tume	Senior Nursing Research Fellow Paediatric ICU	Yes	
Mrs Ann Williams	Lay Member	Yes	

Also in attendance:

<i>Name</i>	<i>Position (or reason for attending)</i>
Mrs Carol Ebenezer	REC Manager
Ms Gemma Warren	REC Assistant

Using the PCI in the identification of fatigue following treatment for head and neck cancer

Rogers SN, Semple C, Humphris GM, Lowe D and Kanatas A

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Trial registration: 32,382. Clinical Trials Identifier, NCT03086629.

Keywords: Fatigue; head and neck cancer; intervention; prompt list; health related quality of life; Patient Concerns Inventory

Abstract

Fatigue has a profound impact on health-related quality of life (HRQOL) and the aim of this study is to describe the clinical characteristics and HRQOL for head and neck cancer patients who raise the issue of fatigue on the Patient Concerns Inventory (PCI), at their review consultation. ~~The data is from a cluster-controlled trial conducted at two UK centres.~~ Eight consultants were randomised to use the PCI as part of a cluster-controlled trial. Patients also completed the UW-QoLv4 (University of Washington Quality of Life), EQ-5D-5L (EuroQol Group) UW-QoLv4 and -Distress Thermometer. thermometer and EQ-5D-5L. There were 140 patients who attended clinics at a median (IQR) of 108 (70-165) days after the end of treatment. The PCI item 'fatigue' was the 6th most commonly selected, by 29% (40). Those with advanced tumours were more likely (36% 30/83 Vs 18% 10/56, $p=0.02$) to have selected the item, as were those treated with radiotherapy +/- chemotherapy (39% 34/87 Vs 11% 6/53, $p<0.001$). The PCI fatigue group reported significantly worse overall QOL, social-emotional and physical function composite scores, distress thermometer ~~score~~, and EQ-5D ~~scores~~. PCI-fatigue was common in those with sleeping, nausea, mood, depression, mobility, breathing and energy level concerns. In conclusion, given the problems associated with fatigue, it is appropriate to screen and seek interventions that might help patient address this.

Introduction

Head and neck cancer (HNC) survivors commonly experience cancer-related fatigue (CRF) and this relates to disease, treatment and individual patient characteristics¹. Moderate and severe fatigue was reported in one fifth of HNC survivors². Cancer-related fatigue compromises survival rates and negatively impacts on activities of daily living (ADLs)³. Fatigue is a barrier to getting back to work⁴. Although the precise mechanism for CRF experienced by HNC survivors is unclear and is probably multi-factorial, radiation to the central nervous system has been implicated, particularly the treatment dose to the brainstem and medulla⁵. Neuroinflammation can also contribute to chronic systemic symptoms such as fatigue, sleep disturbance, chronic widespread pain, mood disorders, neuropsychiatric symptoms, and temperature dysregulation⁶. Patients receiving intensity-modulated radiation therapy (IMRT) seem to have high rates of fatigue, and further research on how inflammation contributes to fatigue is needed⁷. Depression and fatigue symptoms are interlinked and correlate to poor health-related quality of life outcomes (HRQOL)⁸. Evaluation throughout the treatment is important⁹ and fatigue is at its worse around the 6th week of radiation treatment, and slowly improves thereafter¹⁰. Various clinical characteristics associated with worse fatigue have been suggested for example, younger age, previous radiation, depression, and other symptoms such as poor sleep, reduced social activity and cognitive dysfunction^{11, 12}. In a study which utilised the Modified Brief Fatigue Inventory (MBFI), comorbidity and cancer stage were also implicated¹³. It has been suggested that both fatigue and depression should be periodically assessed as both are late effects¹⁴. It is already appreciated that fatigue is an issue that patients wish to talk about in their consultations but little is known about the patient characteristic. Previous reports using the Patient Concerns Inventory (PCI) following HNC treatment has placed fatigue as the 5th most frequent item of the 56 items, being common in early and late stage disease across all sites (oral, oropharyngeal, laryngeal and other)¹⁵.

The aim of this study is to describe the clinical characteristics and HRQOL for those HNC patients who raise the issue of fatigue as something they wish to discuss in their review consultation. Understanding the complexity of CRF as it relates to clinical characteristics and using this knowledge to guide the development of targeted, individualised interventions is critical for reducing the burden of this symptom for HNC survivors.

Method

The methods have been described previously¹⁶. Briefly, the data is from a pragmatic cluster-controlled trial conducted at two UK Cancer Centres, namely Aintree and Leeds. Fifteen consultants (the clustering factor) were randomised, eight to ‘using’ and seven to ‘not using’ an intervention incorporating the PCI prompt list at all their trial clinics. Eligible patients were treated curatively for primary or secondary HNC, and included all sites, stages of disease and treatments. Patients treated palliatively or with recurrence, history of cognitive impairment, psychoses or dementia were excluded. The focus of this paper is to report results from the first ‘baseline’ post-treatment consultation of only the PCI intervention group patients. The PCI prompt list consists of 56 clinical items¹⁷ which patients selected from, at clinic, before seeing their consultant. The patient generated list guides the outpatient consultation and it covers a range of symptoms and potential problems patients may face after treatment. The item relating to fatigue is described as “fatigue/tiredness” on the prompt list, and which in this paper we will simply refer to as “fatigue”. Patients were also asked to select from a list of 18 types of health professional, who they would ‘like to see or be referred to’. Previous work [18] grouped PCI items into four domains: Physical and Functional well-being (29 items), Treatment-related (4 items), Social care/Social well-being (9 items) Psychological and Emotional well-being/Spiritual (14 items).

Clinical and demographic data were collected by a baseline questionnaire or by extraction from electronic records. HRQOL and PCI data were completed electronically (iPAD). HRQOL data included UW-QOLv4¹⁹, Distress thermometer²⁰ and EQ-5D-5L²¹. The UW-QOLv4 questionnaire consists of 12 single question domains, with between 3 and 5 response options scaled evenly from 0 (worst) to 100 (best) according to response hierarchy (Rogers 2002). It also contains a question about overall QOL in which patients are asked to consider not only physical and mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life. Subsequent analysis has led to the development of subscale composite scores²² and domain algorithms to screen for significant problems/dysfunction²³.

The statistical analysis focussed on variables associated with selection of the fatigue item from the PCI prompt list. We considered patient and clinical casemix variables and also a wide range of HRQOL measures. Fishers Exact test was used to compare patient groups regarding selection of the fatigue item. Spearman’s correlation coefficient (r_s) was used to

assess association between the UWQOL activities domain response options and those of the EQ5D-5L usual activities domain. The PCI trial has ethical approval from North West - Liverpool Central Research Ethics Committee REC reference: IRAS 16/NW/0465, Project ID: 189554. It also has approval from the Health Research Authority (HRA). The Research and Development Department at Aintree University Hospital NHS Trust (AUH) is coordinating the trial and AUH is the sponsor for the trial.

Results

Patients recruited to the trial and having baseline data were first discussed at multidisciplinary team (MDT) meetings between January 2017 and December 2018, with first trial clinics between April 2017 and October 2019. Of 288 patients in the trial, 140 were in the PCI intervention group. Clinics were a median (IQR) of 189 (120-255) days after diagnosis and 108 (70-165) after the end of treatment. Characteristics of the 140 PCI group patients can be determined from Table 1.

The mean number of items selected by the 140 PCI patients for discussion in their consultation was 6.60, median (IQR) 5 (2-9), range 0 to 28 with 15 or more items selected by 9% (13). The PCI item 'fatigue' was the 6th most commonly selected, by 29% (40), coming after 'dry mouth' (49%, 68), 'fear of cancer coming back' (34%, 48), 'dental health/teeth' (34%, 48), 'chewing/eating' (33%, 46) and 'salivation' (33%, 46). The longer the consultation the more likely the fatigue item had been selected for discussion (Table 1). Those with advanced tumours were more likely (36% 30/83 Vs 18% 10/56, $p=0.02$) to have selected the fatigue item, as were those having received radiotherapy +/- chemotherapy (39% 34/87 Vs 11% 6/53, $p<0.001$).

Selection of the 'fatigue' item was associated with most of the measured HRQOL variables (Table 2). In particular, there was a clear gradient of selection with overall QOL, ranging from 11% selecting fatigue in patients reporting very good or outstanding QOL to 55% if reporting very poor or poor overall QOL. Clear gradients were seen also regarding the distress thermometer score, the EQ-5D visual analogue scale and EQ-5D TTO crosswalk values. Regarding the UWQOL, this was also evident for both the social-emotional and physical function composite scores. Strong associations were seen with the UWQOL activity domain, the EQ-5D usual activities domain and also with UWQOL recreation, mood, anxiety, saliva and taste domains.

The UWQOL activities domain has five response options, namely, (1) I am usually in bed or chair and don't leave home, (2) I don't go out because I don't have the strength, (3) I am often tired and have slowed down my activities although I still get out (4) There are times when I can't keep up my old pace, but not often and (5) I am as active as I have ever been. Seven patients responded to option 1 or option 2 and 86% (6/7) of these selected fatigue for discussion in their consultation, as did 52% (27/52) for option 3, 11% (4/35) for option 4 and 7% (3/46) for option 5. The EQ5D usual activities domain also has five response options (1) I have no problems doing my usual activities, (2) I have slight problems doing my usual activities, (3) I have moderate problems doing my usual activities, (4) I have severe problems doing my usual activities and (5) I am unable to do my usual activities. Six patients selected option 4 or option 5 and 83% (5/6) selected fatigue, as did 52% (12/23) for option 3, 31% (11/35) for option 2 and 16% (12/76) for option 1. Spearman correlation between the two 5-point measures was $R_s = -0.55$, $p < 0.001$.

Quite clearly the greater the number of PCI items selected the more likely was this number to include fatigue (Table 3), and the same could be said for each of the four PCI domains, and also if health professionals were also selected. Only 2 of the 56 PCI items were not selected by these patients and 4 had very small denominators of under 5 patients; for 48 of the other 50 items the selection of fatigue was higher when that item was selected than when that item was not selected. When sleeping was selected fatigue was also selected in 81% (13/16); higher fatigue selection rates of around 50% and higher were also seen for many variables (Table 3) including nausea (83%, 5/6), mood (83%, 5/6), depression (75%, 6/8), mobility (70%, 7/10), breathing (67%, 6/9) and energy levels (60%, 15/25).

Discussion

CRF following the diagnosis of HNC tends to be under-reported, potentially persistent and of substantial significance to patients, impacting on HRQOL and survival. There are many different aspects including physical, pain, psychological and social factors which contribute to patients' perceived levels of CRF². The PCI is a well reported prompt list^{15,16,18} and as well as allowing a wide range of factors to be considered it is also an holistic approach to delivering patient-centred care. It can be integrated into routine clinics^{24,25}. The specific issue of fatigue reported by the PCI has not previously been assessed in detail, and this novel data has been taken from a cluster randomisation trial involving eight different consultants. The variety of

consultants across two centres, set within the context of routine follow-up consultations means that the findings of this study are pertinent to current practice. The sample comprises of the range of HNC sites managed by head and neck oncology surgeons. The focus of the assessment is around three to six months following completion of treatment. Nautiyal et al¹ reported a dramatic improvement in fatigue levels across the first 3 months post-treatment, followed by a slow improvement over the remainder of the first year, but with higher fatigue levels than those of healthy individuals. Although a fatigue specific questionnaire such as the Modified Brief Fatigue Inventory (MBFI) was not used, the degree of fatigue experienced by the patient will be reflected by the activity and recreation domains of the UW-QOL^{26,27}. There are other factors that might contribute to fatigue such as HPV status as this and inflammation were found to be independent predictors of fatigue over time²⁸. As the PCI can be used at consultations, the prompt of fatigue affords an opportunity for further exploration, plus provision of informal advice and support for both patients and their caregivers. Other unmet needs self-report measures²⁹ or Vanderbilt Head and Neck Symptom survey³⁰ might fulfil a similar purpose.

Over a quarter of the patients wished to talk about fatigue at their consultations. Fatigue was more common when primary treatment related to radiotherapy +/- chemotherapy rather than surgery alone, and expressed by patients with advanced stage. In this sample there was little obvious difference in the frequency that patients wished to talk about fatigue by age, gender, comorbidity and socio-economic group. Those selecting fatigue reported significantly worse QOL, lower scores in the UW-QOL domains apart from appearance, chewing, shoulder and speech. In addition, patients reported worse intimacy, fear of recurrence, distress, and were more likely to report moderate to extreme problems in usual activities (EQ-5D). Fatigue on the PCI was combined with other issues such as appetite, energy levels, sleeping, depression and mood and this reflects the complex nature of inter-related symptoms.

In those patients with CRF, anaemia or hypothyroidism, if present should be corrected and pain control attended to. In our HNC follow-up strategy there is no protocol for routinely checking for anaemia or hypothyroidism. Based on the PCI response and other patient reported outcomes measures that ask about activity, recreation or fatigue, it would be possible to build in an alert such that low scores in these domains triggers the suggestion to the clinician to check the full blood count and thyroxine function test.

It is possible to consider additional interventions. Even though patients might feel too tired to exercise and the symptom persists, there is evidence that if appropriately graded they can

complete an exercise programme, with notable benefits. HNC patients can find it a challenge to exercise²⁷ and prescription should be individually tailored to patient characteristics³¹. A clinic-supported, 12-week progressive strength-training exercise intervention for HNC patients was associated with significant improvements in physical functioning outcomes and improved management of tiredness and fatigue³². Physical exercise interventions demonstrated improvements in physical function, muscular endurance, range of motion, overall quality of life, and showed reductions in pain, and fatigue³³. Progressive resistance training in cachectic HNC patients during radiotherapy seems to be safe and feasible and may have beneficial effects of general fatigue and quality of life³⁴. A home-based personalized behavioural physical activity intervention with fitness graded motion exergames (PAfitME) has been shown to be feasible and acceptable with improvement in CRF, ADL dependence, cardiorespiratory fitness, balance, muscle strength, and shoulder forward flexion³. Another aspect that might make a positive impact is optimisation of nutrition. HNC patients can be malnourished at the time of diagnosis and the side-effects of treatment can exacerbate this through detrimental effects on loss of taste, mucositis, xerostomia, anorexia, nausea and vomiting. Nutritional advice and use of supplements should be used to increase dietary intake and to prevent therapy-associated weight loss³⁵. In nasopharyngeal carcinoma patients, nutrition counselling combined with head and neck rehabilitation exercises greatly reduced fatigue three months after intensity-modulated radiotherapy (IMRT)³⁶. Poor sleep quality is another factor that is related to fatigue and if obstructive sleep apnoea is a contributing factor to sleep disturbance this needs to be addressed³⁷. Interventions aimed at the interaction between the emotional aspects of fatigue and HNC outcomes are appropriate and can have long-term beneficial effects³⁸. In a study of fatigability, depression, and self-esteem among HNC patients, Joseph et al reported that over two thirds of patients had fatigue and a larger proportion suffered from depression¹⁴. The role of social support is vital as it improves emotional adaptation and reduces depressive symptoms. Also, an appreciation of the difficulties involved in social activities exacerbated by a sense of fatigue can result in further social isolation⁸. As the issue of CRF tends to be multi-factorial further research is needed using complex intervention methodology.

In conclusion, a significant proportion of HNC patients following treatment wish to discuss the issue of fatigue during their out-patient consultation. Fatigue is associated with poor outcomes. As fatigue can be a patient concern over an extended period of time, the PCI

prompt list approach could facilitate the discussion during follow-up and allow for further investigation and targeted onward referral based on the aetiology of the fatigue.

Funding sources

This trial is funded by the RfPB on behalf of the NIHR (**PB-PG-0215-36047**).

Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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This study would not have been possible without the valued contribution and support of the eight consultants that used the PCI in the trial.

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Table 1 : Selection of the PCI 'fatigue' item, by casemix

		%	PCI FATIGUE SELECTED Patients	P value**
	Total patients	29	40/140	
Hospital	Aintree	27	22/82	0.70
	Leeds	31	18/58	
Days from diagnosis to first clinic (TERTILES)	≤144	19	9/48	0.16
	125-227	36	16/45	
	≥228	32	15/47	
Days from end of treatment to first clinic (TERTILES)	≤79	29	14/49	0.84
	80-138	26	12/46	
	≥139	31	14/45	
Duration of consultation (minutes) TERTILES	≤8 mins	11	4/37	0.005
	9-12 mins	29	14/49	
	≥13 mins	42	21/50	
Gender	Female	37	18/49	0.12
	Male	24	22/91	
Age	<55	38	11/29	0.48
	55-64	26	16/52	
	65-74	31	10/32	
	≥75	18	3/17	
Tumour site:	Oral cavity	18	10/55	0.10
	Oropharynx	36	15/42	
	Larynx	30	9/30	
	Other	46	6/13	
Overall clinical stage	Advanced 3-4	36	30/84	0.02
	Early 1-2	18	10/56	
Primary treatment*:	S only	13	6/46	0.004
	S only & FF	-	0/7	
	RT or RT/CT only	39	15/38	
	S & (RT or RT/CT)	45	14/31	
	S & (RT or RT/CT) & FF	28	5/18	
WHO comorbidity	0	32	28/88	0.55
	1	25	7/28	
	2-4	21	5/24	
ACE27 comorbidity	None	32	23/71	0.25
	Mild	24	10/41	
	Moderate	20	5/25	
	Severe	67	2/3	
Living situation	Alone in house/flat	17	5/29	0.17
	With others in house/flat	32	35/111	
Working	Yes	29	14/48	>0.99
	No	29	25/86	
Financial benefits	Yes	31	15/49	0.69
	No	27	21/78	
Smoking habit	Current	19	3/16	0.48
	Former	27	22/81	
	Never	34	13/38	
Alcohol habit	Current	24	24/100	0.10
	Former	37	11/30	
	Never	60	3/5	
IMD 2019 quintile	1=least deprived	50	8/16	0.32
	2	28	8/29	
	3	18	4/22	
	4	24	4/17	
	5=most deprived	29	16/56	

* Surgery (S), RadioTherapy (RT), ChemoTherapy (CT), Free Flap transfer (FF)

** Fishers Exact test

Table 2: Selection of the PCI 'fatigue' item, by QOL measures

		PCI FATIGUE SELECTED		P value**
		%	Patients	
All patients		29	40/140	
UWQOL Overall Quality of life	Outstanding/ Very good	11	5/47	0.002
	Good	31	15/48	
	Fair	41	14/34	
	Very Poor / Poor	55	6/11	
Distress thermometer (DT)	Zero	11	4/36	0.02
	1-3	26	10/38	
	4-5	39	13/33	
	6-10	39	13/33	
UWQOL social-emotional subscale	<60	52	13/25	<0.001
	60-79	40	21/53	
	80-100	10	6/62	
UWQOL physical function subscale	<60	39	16/41	0.001
	60-79	36	20/55	
	80-100	9	4/44	
UWQOL items				
<u>Social-emotional subscale</u>				
• Pain	Best possible response	17	9/53	0.05
	Somewhere in-between	33	16/48	
	Dysfunction	38	15/39	
• Activity	Best possible response	7	3/46	<0.001
	Somewhere in-between	36	29/80	
	Dysfunction	57	8/14	
• Recreation	Best possible response	11	7/61	<0.001
	Somewhere in-between	39	28/71	
	Dysfunction	63	5/8	
• Shoulder	Best possible response	26	22/85	0.64
	Somewhere in-between	34	14/41	
	Dysfunction	29	4/14	
• Mood	Best possible response	8	4/48	<0.001
	Somewhere in-between	41	31/75	
	Dysfunction	29	5/17	
• Anxiety	Best possible response	15	7/47	0.003
	Somewhere in-between	29	20/69	
	Dysfunction	54	13/24	
<u>Physical function subscale</u>				
• Appearance	Best possible response	21	9/43	0.41
	Somewhere in-between	31	27/86	
	Dysfunction	36	4/11	
• Swallowing	Best possible response	14	7/50	0.01
	Somewhere in-between	36	26/73	
	Dysfunction	41	7/17	
• Chewing	Best possible response	19	11/57	0.11
	Somewhere in-between	36	23/64	
	Dysfunction	32	6/19	
• Speech	Best possible response	28	18/64	0.68
	Somewhere in-between	27	18/66	
	Dysfunction	40	4/10	
• Taste	Best possible response	12	5/41	0.008
	Somewhere in-between	32	23/72	
	Dysfunction	44	12/27	
• Saliva	Best possible response	12	5/41	0.001
	Somewhere in-between	23	11/47	
	Dysfunction	46	24/52	
Other items:				
• Intimacy	Best possible response	25	27/110	0.04
	Somewhere in-between	50	12/24	
	Dvsfunction	17	1/6	

• Fear of recurrence*	0 or 25	50	8/16	0.01
	50	40	17/43	
	75	21	13/62	
	100	11	2/19	
EQ-5D				
Mobility (walking about)	No problems	25	24/96	0.36
	Slight problems	37	7/19	
	Moderate/severe/unable	36	9/25	
Self-care (washing or dressing myself)	No problems	24	27/113	0.03
	Slight problems	55	6/11	
	Moderate/severe/unable	44	7/16	
Usual activities	No problems	16	12/76	<0.001
	Slight problems	31	11/35	
	Moderate/severe/unable	59	17/29	
Pain (or discomfort)	No pain or discomfort	15	8/54	0.01
	Slight pain or discomfort	33	14/42	
	Moderate/severe/extreme	41	18/44	
Anxiety/depression	Not anxious or depressed	21	14/67	0.01
	Slightly anxious or depressed	29	17/58	
	Moderate/severe/extreme	60	9/15	
EQ-5D-5L TTO crosswalk values (TERTILES)	≤.6950	45	17/38	0.001
	.6951- .8370	31	19/61	
	≥.8371	10	4/41	
EQ5D Visual analogue scale (VAS) TERTILES	≤69	46	21/46	<0.001
	70-81	32	14/44	
	≥82	10	5/50	

*(0) I am fearful all the time that my cancer might return and I struggle with this n=2, (25) I get a lot of fears of recurrence and these can really preoccupy my thoughts n=14, (50) I am sometimes having fearful thoughts but I can usually manage these (75) I have a little fear with occasional thoughts but they don't really bother me (100) I have no fear of recurrence

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Table 3: Selection of the PCI 'fatigue' item and other PCI data

		PCI FATIGUE SELECTED		P value
		%	Patients	
Patients		29	40/140	
No of PCI selected: overall	<5	2	1/57	<0.001
	5-9	30	15/50	
	10-14	65	13/20	
	≥15	85	11/13	
PCI items selected by domain:				
Physical function	<5	8	6/75	<0.001
	5-9	37	16/43	
	≥10	82	18/22	
Cancer treatment	None	24	24/98	0.11
	≥1	38	16/42	
Social care & social wellbeing	None	23	25/109	0.01
	≥1	48	15/31	
Psychological, emotional wellbeing/spiritual	None	11	7/65	<0.001
	1	27	12/44	
	≥2	68	21/31	
No. of Health professionals selected	None	23	17/75	0.05
	≥1	35	23/65	
Other PCI items selected by at least 20% of patients overall	Dry mouth	40	27/68	0.005
	Fear of cancer coming back	48	23/48	<0.001
	Dental health/Teeth	44	21/48	0.006
	Chewing/eating	43	20/46	0.009
	Salivation	48	22/46	0.001
	Swallowing	51	20/39	<0.001
	Taste	42	16/38	0.04
	Sore mouth	45	15/33	0.03
	Mucus	48	16/33	0.007
	Shoulder	45	14/31	0.03
	Pain in the head and neck	57	17/30	<0.001
	Cancer treatment	39	11/28	0.17
Other PCI items*	Activity	50	3/6	0.35
	Appetite	52	14/27	0.004
	Bowel habit	50	6/12	0.10
	Breathing	67	6/9	0.02
	Energy levels	60	15/25	<0.001
	Indigestion	50	3/6	0.35
	Mobility	70	7/10	0.006
	Nausea	83	5/6	0.007
	Pain elsewhere	54	7/13	0.05
	Sleeping	81	13/16	<0.001
	Vomiting	80	4/5	0.02
	Financial benefits	67	4/6	0.06
	Speech/voice/being understood	60	9/15	0.01
	Anxiety	56	9/16	0.02
	Depression	75	6/8	0.007
	Memory	60	6/10	0.03
	Mood	83	5/6	0.007
	Self-esteem	67	4/6	0.06
	Personality & temperament	60	3/5	0.14
	Other Health professionals*	Oral rehab team	57	4/7
Physiotherapy		63	5/8	0.04
Audiologist		50	4/8	0.23

*when these items were selected then Fatigue was selected in at least 50% of the patients. Denominators under 5 were omitted